Remarks

Claims 2-9 were previously pending in the subject application. These claims remain pending and are now before the Examiner for consideration. Favorable consideration of these claims in view of the remarks set forth herein is earnestly solicited.

The applicant wishes to thank Examiner Kim for the courtesy extended to the undersigned during the personal Examiner Interview conducted August 8, 2007. This response and the amendments set forth herein are submitted in accordance with the substance of that interview and constitute a statement of the substance of the interview.

The applicant wishes to thank the examiner for the withdrawal of rejections under §112, first and second, paragraphs.

Claims 2-9 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Fasmer *et al.* of record in view of Williams *et al.* (WO 02/00195) of record. The applicant respectfully traverses this ground for rejection because the cited references, either alone or in combination, do not disclose or suggest the applicant's unique composition, or its intranasal use for the treatment of pain.

The subject invention provides compositions and methods whereby a specific enantiomer of nefopam is administered intranasally for the treatment of pain. While it is true that (+)-nefopam was previously known as an analgesic, nothing in the cited references suggests the advantageous utility of the claimed composition for intranasal administration as claimed by the current applicant.

The Office Action cites the Williams *et al.* reference as providing some teaching with respect to intranasal administration; however, it is clear from a careful reading of the Williams *et al.* disclosure that there would have been no motivation to combine Fasmer *et al.* with Williams *et al.* to arrive at the current invention. Specifically, for example, Williams *et al.* do not teach or even suggest that administration of a composition comprising (+)-nefopam to the mucous membrane of the nasal cavity results in effective delivery of the analgesic to the central nervous system while reducing side effects.

Page 12 of the Williams et al. reference discloses nefopam (the racemate) as one of a long list of analgesics. This list includes over 100 analgesics, none which are identified as being useful for intranasal delivery. The Williams *et al.* reference also includes similar long lists of opiods, local

anesthetics, mucoadhesives, preservatives, chelating agents, acids, bases, buffers, receptor antagonists, excipients, antibiotics, antifungal agents, anti-inflammatory agents, antitussive agents, expectorants, glucocorticoids, vitamins, anti-oxidants, flavoring agents, and sweetening agents (see pages 4 to 14 of the Williams *et al.* reference).

Certainly, it would not be obvious to use each and every one of the thousands of compounds mentioned by Williams *et al.* (including each and every enantiomer) for intranasal administration. Therefore, to support an obviousness rejection the Office Action must identify additional teachings that would direct the person skilled in the art to the particular advantageous composition and use claimed by the current applicant.

The predecessor of the Federal Circuit has opined, "[i]n determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972). Therefore, "[w]hen determining the patentability of a claimed invention which combines two known elements, 'the question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.' " See *In re Beattie*, 974 F.2d 1309, 1311-12, 24 USPQ2d 1040, 1042 (Fed. Cir. 1992) (quoting *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1462, 221 USPQ 481, 488 (Fed. Cir. 1984)). Finally, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

Williams *et al.* provide no suggestion that <u>any</u> of the listed compounds is particularly suitable for intranasal delivery. In this regard, please note that the Williams *et al.* reference describes administration to mucosal surfaces other than nasal mucous membranes and, in fact, the emphasis of the Williams *et al.* disclosure is on the treatment of oral mucositis. Even the Williams *et al.* passage cited in the Office Action in which Williams *et al.* refer to chemotherapy is clearly describing <u>oral</u> mucositis.

Therefore, even to the extent that a skilled artisan might identify a particular compound amongst the thousands of compounds listed by Williams *et al.*, it would clearly not be possible to draw any inference about the suitability of that particular compound for intranasal delivery. Accordingly, there is no reason to combine the Fasmer *et al.* reference with the Williams *et al.* reference to arrive at a composition that is particularly well suited for intranasal administration.

Even if Williams *et al.* and Fasmer *et al.* were combined (a combination that requires the extremely unlikely selection of nefopam as the analgesic, (+)-nefopam as the enantiomer of interest, and assumes that administration to the nasal cavity is intended), the resultant composition would comprise, in addition to (+)-nefopam, the local anesthetic and the opioid that are essential components as described by Williams *et al.* Further, even if this unlikely selection were made, the intention of Williams *et al.* is to treat a local problem, i.e., mucosal inflammation, abrasions, ulcerations, lesions, trauma or incisions.

Unlike the Williams *et al.* method for treating a local problem, the compositions and methods of the subject invention advantageously deliver significant concentrations of (+)-nefopam to the central nervous system (CNS), while reducing side-effects. Fortuitously, the methods of the subject invention, avoid first-pass metabolism and reduce peripheral exposure to vascular smooth muscle. The methods of the subject invention find particular applicability to treat certain conditions, such as cancer as is set forth in claim 8. The advantageous delivery of significant concentrations of (+)-nefopam to the CNS is even achieved at low dosages as set forth in, for example, claim 9.

As noted above, the emphasis of Williams *et al.* is on the treatment of local oral mucositis. It is certainly the intention of Williams *et al.* to achieve local application and effect, and not to deliver active ingredient to the CNS. By contrast, the present invention achieves advantageous and safe administration of (+)-nefopam to the CNS.

It has been well established in the patent law that the mere fact that an applicant's invention contains known elements does not make the invention obvious unless there is "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR Intrnational Co. v. Teleflex Inc.*, 550 U.S. ___ (2007).

Furthermore, an applicant's invention is not "proved obvious merely by demonstrating that each of its elements was, independently, known in the (purported) prior art." *Id.*

An assertion of obviousness without the required suggestion or expectation of success in the prior art is tantamount to using applicant's disclosure to reconstruct the prior art to arrive at the subject invention. Hindsight reconstruction of the prior art cannot support a §103 rejection, as was specifically recognized by the CCPA in *In re Sponnoble*, 56CCPA 823, 160 USPQ 237, 243 (1969).

On page 6 of the Office Action, it is stated that "Williams *et al.* teach that nefopam comprising formulation in general are preferably applied directly to nasal cavity." The applicant has been unable to identify any such general teaching in the Williams *et al.* reference. Rather Williams *et al.* emphasize application of their composition to oral mucosal surfaces. The next sentence of the Office Action refers to the "preferred route of administration of nefopam known in the art as taught by Williams *et al.*"; clearly Williams *et al.* do not provide any such teaching.

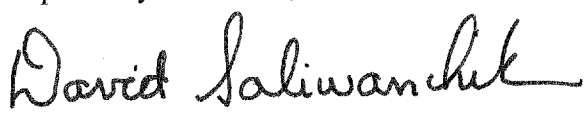
Also at page 6, the Office Action states that "Williams *et al.* teach the pH suitable for intranasal application." Again, this characterization of the Williams *et al.* reference very significantly overstates the teachings of that reference with respect to intranasal administration. Williams *et al.* teach nothing particular about either (+)-nefopam or intranasal administration. In summary, Williams *et al.*, even in combination with Fasmer *et al.*, give no motivation to choose nefopam in particular, and no reason whatsoever to choose (+)-nefopam for application to the nasal cavity as claimed by the current applicant. Therefore, the applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. §103 based on Fasmer *et al.* in view of Williams *et al.*

In view of the foregoing remarks and the amendment above, the applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

The applicant also invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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